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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.53 (c).

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INVENTOR(s)/APPLICANT(s)

Given Name (first and middle [if any])	Last Name	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
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☐ Additional inventors are being named on the separately numbered sheets attached hereto

TITLE OF THE INVENTION (280 characters max)

NOVEL AMINOBENZOPHENONE COMPOUNDS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☐ Application Data Sheet. See 37 CFR 1.76.
☐ Other (specify):____

METHOD OF PAYMENT *(check one)*	PROVISIONAL FILING FEE
☐ Applicant claims small entity status. See 37 CFR 1.27.	☐ Small Entity ($80.00)
☒ A check or money order is enclosed to cover the Provisional filing fees.	☒ Large Entity ($160.00)
☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number 02-2448, if necessary.	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

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ADM/csm
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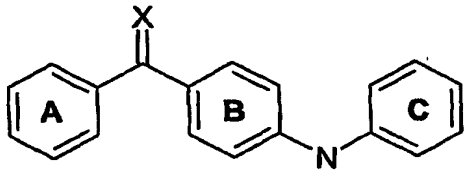
NOVEL AMINOBENZOPHENONE COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to a novel type of aminobenzophenones and to their use in therapy.

BACKGROUND OF THE INVENTION

Aminobenzophenones are well known from the scientific as well as the patent literature. Thus, WO 98/32730, WO 01/05746, WO 01/05749, WO 01/05751, WO 01/05744 and WO 01/05745 all disclose compounds with the common core structure



wherein the phenyl ring C is substituted by amine derivatives. Moreover, WO 01/42189 and WO 02/076447 disclose compounds with a similar structure, but with no nitrogen substituent in phenyl ring C. Finally, WO 01/90074 and WO 02/083622 disclose compounds where the phenyl rings A and C respectively are replaced by heterocycles. The compounds disclosed in these patent application are indicated to be inhibitors of interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) secretion *in vitro*, which makes the compounds potentially useful in the treatment of inflammatory diseases where the production of cytokines is involved in the pathogenesis. Allegedly, aminobenzophenones exert their effect by inhibiting the p38 MAP kinase, which in turn inhibits the production of IL-1β and TNF-α.

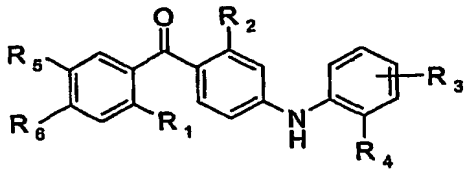
The preparation of structurally related aminobenzophenones useful as dyes for textiles is disclosed in Man-Made Text. India (1987), 30(6), 275-6, Man-Made Text. India (1986), 29(5), 224-30, and Man-Made Text. India (1985), 28(11), 425, 427-9, 431.

SUMMARY OF THE INVENTION

It has surprisingly been found that novel aminobenzophenone derivatives are potent inhibitors of interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) secretion *in vitro*, suggesting their utility in the treatment and/or prevention of inflammatory diseases and other conditions where the secretion and modulation of proinflammatory cytokines is involved in the pathogenesis.

It has been found that aminobenzophenone derivatives of the present invention exert their anti-inflammatory effect by inhibiting or downregulating MAP kinases, more specifically the p38 MAP kinase, a stress-activated protein which is an important element of the signal transduction pathway leading to the production of proinflammatory cytokines. The aminobenzophenone derivatives of the present invention may furthermore be useful in the treatment of cancer.

Accordingly, the present invention relates to a compound of general formula I



I

wherein

R_1 is halogen, hydroxy, mercapto, trifluoromethyl, amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4} alkylthio, C_{1-6}alkylamino, C_{1-4}alkoxycarbonyl, cyano, $-CONH_2$ or nitro;

R_2 is halogen, hydroxy, mercapto, trifluoromethyl, amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-6}alkylamino, C_{1-4}alkoxycarbonyl, cyano, $-CONH_2$, phenyl or nitro;

R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, cyano, carboxy, $CONH_2$, nitro, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkylthio, and C_{1-4} alkoxycarbonyl;

R_4 is hydrogen, halogen, R_8 or Y_1R_8;

Y_1 is $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-NR_a-$, $-NR_aC(O)NR_b-$, $-NR_aC(O)-$, $-C(O)NR_a-$, $-C(O)NR_aO-$, $-C(O)-$, $-C(O)O-$, $-NR_aC(O)O-$, $-S(O)_2NR_a-$, $-NR_aS(O)_2-$;

R_a and R_b are the same or different, each representing hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-8}carbocyclyl, C_{3-8}heterocyclyl or aryl;

R_8 is hydrogen, C_{1-10}alkyl-heterocyclyl, C_{1-10}alkyl-C_{3-12}carbocyclyl, C_{1-10}alkyl, C_{2-10}alkenyl,

C_{2-10} alkynyl, C_{3-12}carbocyclyl or heterocyclyl; each of which being optionally substituted by one or more, same or different substituents represented by R_7;

R_7 is halogen, hydroxy, mercapto, trifluoromethyl, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-6} alkylamino, C_{1-4}alkoxycarbonyl, C_{1-9} trialkylammonium in association with an anion, cyano, azido, nitro, -COOH, $-CONH_2$, -CONHR' or -CONRR', wherein R and R' are same or different, each representing hydrogen or C_{1-3}alkyl;

one of R_5 and R_6 is Y_2R_9, C_{1-6}alkyl-Y_2R_9, C_{1-6}alkenyl-Y_2R_9, C_{1-10}alkyl-heterocyclyl, C_{1-10}alkyl-C_{3-12}carbocyclyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10} alkynyl, C_{3-12}carbocyclyl or C_{3-12}heterocyclyl, each of which being optionally substituted by one or more, same or different substituents represented by R_7, and the other is hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4} alkylthio, C_{1-6}alkylamino, C_{1-4}alkoxycarbonyl, cyano, $-CONH_2$ or nitro,

with the proviso that when R_5 or R_6 is phenyl, C_{1-5}alkyl or C_{2-3}alkenyl, it is substituted by one or more, same or different substituents represented by R_7 (except fluorine when R_5 or R_6 is methyl);

Y_2 is -O-, -S-, -S(O)-, $-S(O)_2-$, $-NR_a-$, $-NR_aC(O)NR_b-$, $-NR_aC(O)-$, $-C(O)NR_a-$, $-C(O)NR_aO-$, -C(O)-, $-NR_aC(O)O-$ or $-NR_aS(O)_2-$;

R_9 is C_{1-10}alkyl-heterocyclyl, C_{1-10}alkyl-C_{3-12}carbocyclyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10} alkynyl, C_{3-12}carbocyclyl or C_{3-12}heterocyclyl, each being optionally substituted by one or more, same or different substituents represented by R_7, with the proviso that when Y_2 is $-O-$, $-NR_a-$ or $-S-$, and R_9 is C_{1-6}alkyl, it is substituted by one or more, same or different substituents represented by R_7;

or, when one of R_5 or R_6 is the group $-C(O)NR_aR_9$, R_a and R_9 together with the nitrogen atom to which they are attached form a heterocyclic ring optionally comprising one or more additional heteroatoms selected from the group consisting of O, S and N, optionally substituted with one or more substituents represented by R_7;

or a pharmaceutically acceptable salt, solvate, or ester thereof.

In another aspect, the invention relates to a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, or ester thereof together with a pharmaceutically acceptable excipient or vehicle.

In a further aspect, the invention relates to a method of preventing, treating or ameliorating inflammatory diseases or conditions, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I.

In a further aspect, the invention relates to a method of treating or ameliorating cancer, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I.

In a still further aspect, the invention relates to the use of a compound of formula I for the manufacture of a medicament for the prophylaxis, treatment or amelioration of inflammatory diseases or conditions.

In a still further aspect, the invention relates to the use of a compound of formula I for the manufacture of a medicament for the treatment or amelioration of cancer.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

In the present context, the term "alkyl" is intended to indicate a univalent radical derived from straight or branched alkane by removing a hydrogen atom from any carbon atom. The alkyl chain typically comprises 1-10 carbon atoms, in particular 1-6 carbon atoms. The term includes the subclasses normal alkyl (*n*-alkyl), secondary and tertiary alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec.*-butyl, *tert.*-butyl, pentyl, isopentyl, hexyl and isohexyl.

The term "alkoxy" is intended to indicate a radical of formula OR', wherein R' is alkyl as defined above, e.g. methoxy, ethoxy, propoxy, butoxy, etc.

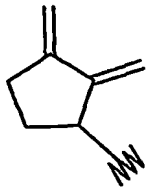
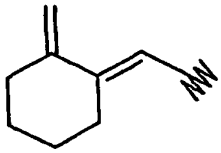
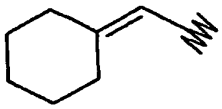
The term "alkenyl" is intended to indicate a mono-, di-, tri-, tetra- or pentaunsaturated hydrocarbon radical typically comprising 2-10 carbon atoms, in particular 2-6 carbon atoms, e.g. ethenyl, propenyl, butenyl, pentenyl or hexenyl. The term "alkynyl" is intended to indicate an hydrocarbon radical comprising 1-5 triple C-C bonds, the alkyne chain typically

comprising 2-10 carbon atoms, in particular 2-6 carbon atoms, such as ethynyl, propynyl, butynyl, pentynyl or hexynyl.

The term "alkoxycarbonyl" is intended to indicate a radical of formula –COOR' wherein R' is alkyl as defined above, e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, etc.

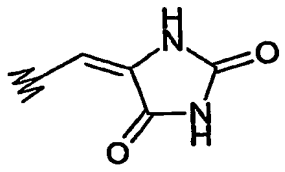
The term "aryl" is intended to include radicals of carbocyclic aromatic rings, in particular 5- or 6-membered rings, optionally fused bicyclic rings, e.g. phenyl or naphthyl. The term "heteroaryl" is intended to include radicals of heterocyclic aromatic rings, in particular 5- or 6-membered rings with 1-4 heteroatoms selected from O, S and N, or optionally fused bicyclic rings with 1-4 heteroatoms, e.g. pyridyl, tetrazolyl, thiazolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thienyl, pyrazinyl, isothiazolyl, benzimidazolyl and benzofuranyl.

The term "carbocyclyl" includes saturated and unsaturated, optionally fused bicyclic, hydrocarbon rings typically comprising 3-12 carbon atoms, in particular 3-8 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl and cyclooctyl; or a C_{3-12} cycloalkene group, such as cycloprop-2-enyl, cyclobut-2-enyl, cyclopent-2-enyl, cyclohex-3-enyl, cycloocta-4-enyl, cyclohex-3,5-dienyl, indanyl, indeneyl, 1,4-dihydronaphtyl, phenyl and naphtyl. The term "carbocyclyl" also includes cyclic hydrocarbons wherein one or more ring $-CH_2-$ fragments have been replaced by a –C(O)- fragment and /or an exo-cyclic carbon-carbon double bond, such as oxocyclohexyl, oxocyclopentyl, 4-oxo-1,2,3,4-tetrahydronaphtalen-1-yl, 1-oxo-1,2,3,4-tetrahydronaphtalen-1-yl, 2-oxocyclohex-3-en-1-yl and 2-oxocyclohex-1-en-1-yl, and

The term "heterocyclyl" is intended to indicate saturated or unsaturated, optionally fused carbocyclic rings comprising 3-12 carbon atoms, in particular 3-8 carbon atoms, and comprising one or more heteroatoms selected from the group consisting of O, N and S, such as pyrrolyl, furanyl, morpholyl, piperazyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, tetrahydrotiophenyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, putinyl, quinolinyl, isoquinolinyl, 1,2-dihydroquinolinyl, etc.

The term "heterocyclyl" also includes heterocyclic groups wherein one or more ring $-CH_2-$ fragments have been replaced by a –C(O)- fragment and/or an exo-cyclic carbon-carbon double bond, such as dioxopiperidinyl, 1-oxo-3,4-dihydroisoquinolin-2(1H)-yl and



The term "alkylthio" is intended to indicate a radical of the formula -SR, where R is alkyl as defined above, for example C_{1-10}alkylthio, C_{1-4}alkylthio, methylthio, ethylthio, *n*-propylthio, 2-propylthio, etc.

The term "alkylamino" is intended to indicate a radical of the formula -NHR or $-NR_2$, wherein R is alkyl as defined above and includes, for example, methylamino, dimethylamino, di-(n-propyl)amino, *n*-butyl(ethyl)amino, etc.

The term "halogen" is intended to indicate fluoro, chloro, bromo or iodo.

The term "pharmaceutically acceptable salt" is intended to indicate salts prepared by reacting a compound of formula I with a suitable inorganic or organic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, phosphoric, formic, acetic, 2,2-dichloroaetic, adipic, ascorbic, L-aspartic, L-glutamic, galactaric, lactic, maleic, L-malic, phthalic, citric, propionic, benzoic, glutaric, gluconic, D-glucuronic, methanesulfonic, salicylic, succinic, malonic, tartaric, benzenesulfonic, ethane-1,2-disulfonic, 2-hydroxy ethanesulfonic acid, toluenesulfonic, sulfamic or fumaric acid. Pharmaceutically acceptable salts of compounds of formula I may also be prepared by reaction with a suitable base such as sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, ammonia or the like.

The term "solvate" is intended to indicate a species formed by interaction between a compound, e.g. a compound of formula I, and a solvent, e.g. alcohol, glycerol or water, wherein said species are in a solid form. When water is the solvent, said species is referred to as a hydrate.

The term "pharmaceutically acceptable ester" is intended to indicate easily hydrolysable esters such as alkanoyloxyalkyl, aralkanoyloxyalkyl, aroyloxyalkyl, e.g. acetoxymethyl, pivaloyloxymethyl, benzoyloxymethyl esters and the corresponding 1'-oxyethyl derivatives, or alkoxycarbonyloxyalkyl esters, e.g. methoxycarbonyloxymethyl esters and ethoxycarbonyloxymethyl esters and the corresponding 1'-oxyethyl derivatives, or lactonyl esters, e.g. phthalidyl esters, or dialkylaminoalkyl esters, e.g. dimethylaminoethyl esters. Easily hydrolysable esters include *in vivo* hydrolysable esters of the compounds of formula I. Such esters may be prepared by conventional methods known to persons skilled in the art, such as method disclosed in GB patent No. 1 490 852 incorporated herein by reference.

"p38 MAP kinase" is a stress-activated protein kinase existing in several isoforms (p38α, p38β, p38β2, p38γ and p38δ). The p38 MAP kinase is activated by different stimuli including heat, chemical, osmotic, pH and oxidative stress, growth factor withdrawal, high or low glucose and ultraviolet radiation. p38 is also stimulated by agents that mediate the initial physiological response to injury, infection and inflammation, such as LPS and pro-inflammatory cytokines IL-1β, TNF–α, FasL, CD40L and TGF-β. Like other MAP kinases, p38 is phosphorylated by kinases, including MKK3, MEK6 and MKK6, on a threonine and tyrosine in an activation loop (Thr-Xaa-Tyr) close to the ATP and substrate binding site. In turn, p38 phosphorylates and activates the serine-threonine protein kinases MAPKAP kinase-2, MAPKAP kinase-3, MAPKAP kinase-5, MNK-1 and MSK-1. It has been established that activation of p38 regulates cytokine biosynthesis in many cell types either directly by phosphorylating and activating transcription factors involved in the expression of cytokines or indirectly, e.g. by phosphorylating MSK-1 which, when activated, activates the transcription factor CREB. It has also been shown that certain pyridinyl imidazoles, e.g. SB203580, which inhibit p38, inhibit the production of IL-1β and TNF–α from LPS-treated human monocytes. It has therefore been concluded that p38 constitutes a potentially highly interesting target for the development of anti-inflammatory compounds (cf. JC Lee et al., *Immunopharmacology 47*, 2000, pp. 185-201 and references reviewed therein; PR Young, "Specific Inhibitors of p38 MAP kinase" in *Signaling Networks and Cell Cycle Control: The Molecular Basis of Cancer and Other Diseases*, JS Gutkind (Ed.), Humana Press, Inc., Totowa, NJ, and references reviewed therein).

There are several reports on p38 MAP kinase and inflammatory cytokines in relation to cell growth and apoptosis, such as tumor proliferation and metastasis. Though the exact mechanism of p38 MAP kinase mediated cell growth regulation is not known, it is believed that p38MAP kinase constitutes a potentially highly interesting target for the development of anti cancer drugs (S Nakada et al., Anticancer Research *21(1A)*, 2001, pp.167-171 and

references cited therein; C Denkert et al., Cancer Letters *195(1)*, 2003 p.p. 101-109 and references cited therein).

Compounds of formula I may comprise asymmetrically substituted (chiral) carbon atoms and carbon-carbon double bonds which may give rise to the existence of isomeric forms, e.g. enantiomers, diastereomers and geometric isomers. The present invention relates to all such isomers, either in pure form or as mixtures thereof. Pure stereoisomeric forms of the compounds and the intermediates of this invention may be obtained by the application of procedures known in the art. Diastereomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e. g. liquid chromatography using chiral stationary phases. Enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereoisomeric forms may also be derived from the corresponding pure stereoisomeric forms of the appropriate starting materials, provided that the reaction occurs stereoselectively or stereospecifically. Preferably, if a specific stereoisomer is desired, said compound will be synthesized by stereoselective or stereospecific methods of preparation. These methods will advantageously employ chiral pure starting materials. Likewise, pure geometric isomers may be obtained from the corresponding pure geometric isomers of the appropriate starting materials. A mixture of geometric isomers will typically exhibit different physical properties, and they may thus be separated by standard chromatographic techniques well-known in the art.

Preferred embodiments of the compound of formula I

In a currently preferred embodiment of the compounds of formula I, R_1 may be halogen, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or nitro. In particular, R_1 may be methyl, ethyl, methoxy, ethoxy, bromo, fluoro or chloro.

In a further preferred embodiment of the compounds of formula I, R_2 may be halogen, amino, C_{1-4}alkyl or C_{1-4}alkoxy. In particular, R_2 may be methyl, ethyl, methoxy, ethoxy, bromo, fluoro or chloro.

In a further preferred embodiment of the compounds of formula I, R_3 may be hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy. In particular, R_3 may be methyl, ethyl, methoxy, ethoxy, bromo, fluoro or chloro.

In a further preferred embodiment of the compounds of formula I, Y_1 may be -O-, -NR_a-, -$NR_aC(O)NR_b$-, -$NR_aC(O)$-, -$C(O)NR_a$- or -$NR_aC(O)O$-.

In a further preferred embodiment of the compounds of formula I, R_8 may be C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl.

In a further preferred embodiment of the compounds of formula I, R_7 may be halogen, hydroxy, amino, C_{1-4}alkoxy, C_{1-4}alkyl, C_{1-4}alkylamino, C_{1-4}alkoxycarbonyl, -COOH, -$CONH_2$, -CONR' or –CONRR', wherein R and R' are as defined above.

In a further preferred embodiment of the compounds of formula I, one of R_5 and R_6 may be Y_2R_9, C_{1-4}alkyl-Y_2R_9, C_{1-4}alkenyl-Y_2R_9, C_{1-4}alkyl-C_{3-6}heterocyclyl, C_{1-4}alkyl-C_{3-6}carbocyclyl, C_{1-4}alkyl substituted by R_7, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl, and the other is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy. In particular, R_5 may be Y_2R_9, C_{1-4}alkyl-Y_2R_9, C_{1-4}alkenyl-Y_2R_9, C_{1-4}alkyl-C_{3-6}heterocyclyl, C_{1-4}alkyl-C_{3-6}carbocyclyl, C_{1-4}alkyl substituted by R_7, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl, and R_6 may be hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy. More preferably, R_6 is hydrogen.

In a further preferred embodiment of the compounds of formula I, Y_2 may be -O-, -NR_a-, -$NR_aC(O)NR_b$-, -$NR_aC(O)$-, -$C(O)NR_a$-, -$C(O)NR_aO$-, -C(O)- or -$NR_aC(O)O$-.

In a further preferred embodiment of the compounds of formula I, R_9 may be C_{1-4}alkyl-C_{3-6} heterocyclyl, C_{1-4}alkyl-C_{3-6}carbocyclyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl.

In a particularly preferred embodiment of the compounds of formula I,

R_1 is halogen, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or nitro;

R_2 is halogen, amino, C_{1-4}alkyl or C_{1-4}alkoxy;

R_3 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy;

Y_1 is –O-, -NR_a-, -$NR_aC(O)NR_b$-, -$NR_aC(O)$-, -$C(O)NR_a$- or -$NR_aC(O)O$-;

R_8 is C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl;

R_7 is halogen, hydroxy, amino, C_{1-4}alkoxy, C_{1-4}alkyl, C_{1-4}alkylamino, C_{1-4}alkoxycarbonyl, -COOH, -$CONH_2$, -CONR' or –CONRR', wherein R and R' are as indicated above;

R_5 is Y_2R_9, C_{1-4}alkyl-Y_2R_9, C_{1-4}alkenyl-Y_2R_9, C_{1-4}alkyl-C_{3-6}heterocyclyl, C_{1-4}alkyl-C_{3-6}carbocyclyl, C_{1-4}alkyl substituted by R_7, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl, and R_6 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy;

Y_2 is -O-, -NR_a-, -$NR_aC(O)NR_b$-, -$NR_aC(O)$-, -$C(O)NR_a$-, -$C(O)NR_aO$-, -C(O)- or -$NR_aC(O)O$-; and

R_9 is C_{1-4}alkyl-C_{3-6} heterocyclyl, C_{1-4}alkyl-C_{3-6}carbocyclyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl.

Specific examples of compounds of formula I may be selected from the group consisting of

[2-Chloro-4-(4-fluoro-2-methylphenylamino)phenyl]-[2-methyl-5-(morpholine-4-carbonyl)phenyl]methanone (Compound 101),

[2-Chloro-4-(4-fluoro-2-methylphenylamino)phenyl]-[2-methyl-5-(4-methylpiperazine-1-carbonyl)phenyl]methanone (Compound 102),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-*N*-methoxy-4,*N*-dimethylbenzamide (Compound 103),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-(tetrahydrofuran-2-ylmethyl)benzamide (Compound 104),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4,*N*-dimethyl-*N*-(tetrahydrofuran-2-ylmethyl)benzamide (Compound 105),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-*N*-(2-methoxyethyl)-4-methylbenzamide (Compound 106),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-(3-morpholin-4-ylpropyl)benzamide (Compound 107),

[2-Chloro-4-(4-fluoro-2-methylphenylamino)phenyl]-{5-[4-(2-methoxyethyl)piperazine-1-carbonyl]-2-methylphenyl}methanone (Compound 108),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-pyridin-4-ylmethylbenzamide (Compound 109),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-pyridin-2-ylmethylbenzamide (Compound 110),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-pyridin-3-ylmethylbenzamide (Compound 111),

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 112),

3-[4-(2-Amino-4-bromophenylamino)-2-chlorobenzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 113),

3-[4-(4-Bromo-2-methylphenylamino)-2-chlorobenzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 114),

3-[2-Chloro-4-(2,4-difluorophenylamino)benzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 115),

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-(2-methoxyethyl)-4-methylbenzamide (Compound 116),

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-ethyl-4-methylbenzamide (Compound 117),

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-(3-hydroxypropyl)-4-methylbenzamide (Compound 118), and

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 119).

In addition to the definition of R_4 indicated above, it is envisaged that R_4 may include substituents included in the definition of R_6 in WO 03/018535, the content of which is hereby incorporated by reference in its entirety.

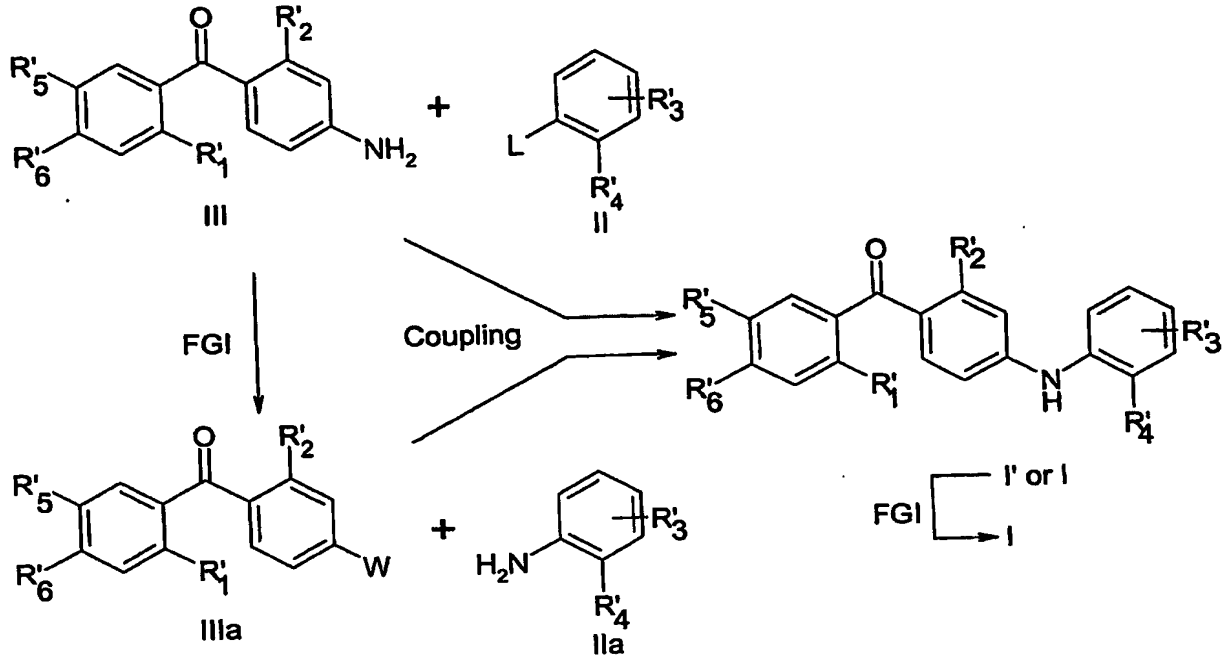
It is further envisaged that the compounds of formula I may be *N*-substituted at the amino group between rings B and C of the core structure, using substituents substantially as disclosed in US Provisional Application No. 60/434,798, the content of which is hereby incorporated by reference in its entirety.

Methods of preparation

The compounds of the present invention may be prepared in a number of ways well known to those skilled in the art of organic synthesis. The compounds of the present invention can be synthesised using the methods outlined below, together with methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below.
The compounds of formula I may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents that are appropriate with respect to the reagents and materials employed and that are suitable for the transformations being effected. Also, in the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of experiment and work-up procedures, are chosen to be conditions of standard for that reaction, which should be readily recognised by one skilled in the art. It is understood by one skilled in the art of organic synthesis, that the functionality present on various positions of the molecules used as the starting compounds or intermediates in the syntheses, must be compatible with the reagents and reactions proposed. Not all compounds of formula I falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions of substituents or functional groups which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods can be used.

Compounds according to the present invention may be prepared by a process comprising coupling of an amine of formula III with a triflate or halide, such as a bromide, iodide, fluoride, chloride, of formula II, as shown in Scheme 1; or alternatively by a process comprising coupling of an amine of formula IIa with a triflate or halide, such as a bromide or iodide, of formula IIIa, as shown in Scheme 1; where R_1, R_2, R_3, R_4, R_5, and R_6 are as defined above; except that any substituents or functional groups which are potentially

reactive in the coupling reaction may be protected before the coupling reaction is performed, and the protective groups removed subsequently.



L: Br, I, OSO_2CF_3, or F and Cl (in special cases e.g. when R'_4 is EWG like NO_2)
W: Br, I, or OSO_2CF_3
FGI: Functional group interconversion
R'_1, R'_2, R'_3, R'_4, R'_5, and R'_6 stands for R_1, R_2, R_3, R_4, R_5, and R_6 respectively or any suitable FG (functional group) which may be transformed to R_1, R_2, R_3, R_4, R_5, and R_6

Scheme 1

The coupling reaction is carried out by using a method for the formation of diphenylamines well known to one skilled in the art of organic synthesis. The preferred method is the palladium catalysed amination method which comprises coupling of an amine with an arylhalogenide (or aryltriflate) in the presence of a base, a suitable Pd source, and a suitable phosphine ligand in an inert solvent.
Different palladium compounds may be used in the process, non-limiting examples of which are palladium(II) acetate, palladium(II) chloride, palladium(II) bromide, dichlorobis(triphenylphosphine)palladium(II), tetrakis(triphenylphosphine)palladium(0), tris(dibenzylideneacetone)dipalladium(0). The preferred phosphine ligands include, but are not limited to, racemic or non-racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (hereinafter refered to as BINAP), tri-*o*-tolylphosphine, tri-*tert*-butylphosphine, 1,1'-

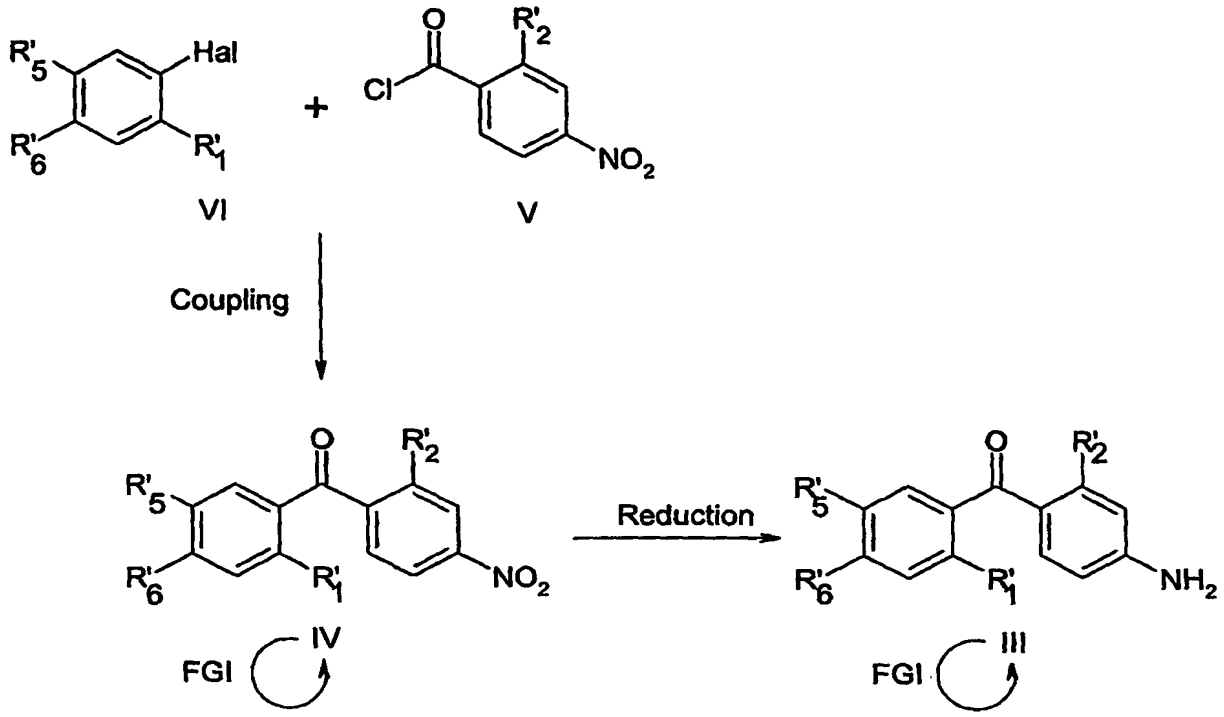
bis(diphenylphosphino)-ferrocene, bis[(2-diphenylphosphino)phenyl]ether (DPEphos), 2-dicyclohexylphosphanyl-2'-dimethylaminobiphenyl, 2-(di-*tert*-butylphosphino)biphenyl and 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene (Xantphos). The amount of palladium and ligand used in this catalytic process is typically in the range 0.1 to 10 % by mole relative to the amount of the aromatic halide (or triflate) used.

Especially sodium-*tert*-butoxide (NaO*t*-Bu) and caesium carbonate (Cs_2CO_3) have proven to be the preferred bases in this process, but other bases may be used as well.

The reaction is typically performed at elevated temperatures (80-120 ^oC) in inert solvents such as 1,4-dioxane, toluene, benzene, and tetrahydrofuran under an inert atmosphere, e.g. argon or nitrogen.

When R'_4 is an electron withdrawing group (EWG) such as nitro or cyano the above coupling may also be performed non-catalytically in the presence of strong bases like potassium- or sodium-*tert*-butoxide. The reaction is typically performed at room temperature or higher (20-200 ^oC) in aprotic solvents like dimethylsulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF) or *N*-methylpyrrolidinone (NMP) under an inert atmosphere, e.g. argon or nitrogen.

Compounds according to the present invention of the general formula III may be prepared by several methods known to those skilled in the art of organic synthesis. One useful sequence is shown in Scheme 2. The key step comprises the coupling of a halide, preferably an iodide or bromide of general formula VI with an acid chloride of general formula V to afford a benzophenone of general formula IV. The benzophenone IV may then be reduced to the corresponding amine of general formula III by treatment with standard reducing agents. Examples of such reducing agents include, but are not limited to, stannous chloride dihydrate, hydrogen, ammonium formiate or hydrazine hydrate and a catalytic amount of palladium on carbon. The coupling reaction is done by transforming the halide (VI) into a reactive organometallic intermediate, such as by treatment with *iso*-propyl magnesium chloride to afford the corresponding magnesium derivative, or by treatment with n-butyllithium to afford the corresponding lithium derivative.

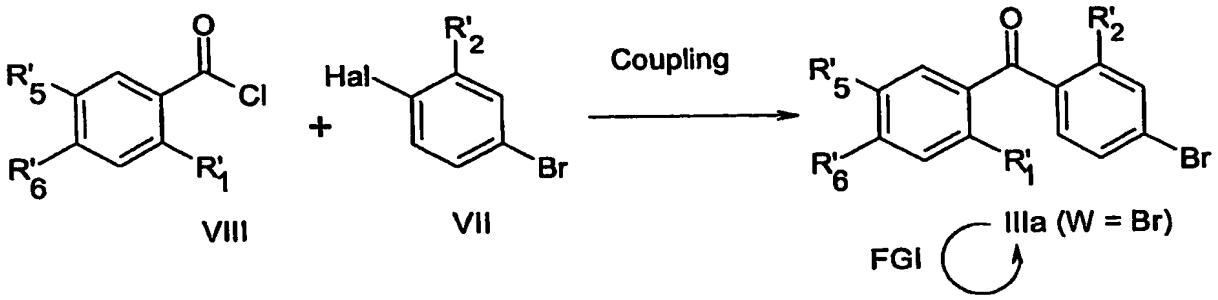


Hal: I or Br
FGI: Functional group interconversion
R'_1, R'_2, R'_5, and R'_6 stands for R_1, R_2, R_5, and R_6 respectively or any suitable FG (functional group) which may be transformed to R_1, R_2, R_5, and R_6

Scheme 2

The reactivity of this organometallic intermediate is then modulated by transmetalation to e.g. zinc, by treatment with $ZnCl_2$, $ZnBr_2$, or ZnI_2. This organozinc compound is then coupled with the acid chloride of general formula V, mediated by a catalytic amount of a palladium(0) complex. Examples of such palladium catalysts include but are not limited to tetrakis(triphenylphosphine)palladium(0), tetrakis(triphenylarsine)palladium(0), dichlorobis(triphenylphosphine)palladium(II), or benzylchlorobis(triphenylphosphine)palladium(II). Alternatively, the organozinc compound is coupled with the acid chloride, of general formula V, mediated by a catalytic amount of copper salts, such as copper(II)acetate or the soluble complex CuCN·2LiCl. The coupling reaction is typically performed at room temperature in inert solvents such as 1,4-dioxane, toluene, benzene, and tetrahydrofuran under an inert atmosphere, e.g. argon or nitrogen.

Compounds accordingly to the present invention of general formula IIIa may be prepared by analogous zinc mediated cross-coupling procedures as shown in Scheme 3.



Hal: I or Br
FGI: Functional group interconversion
R'_1, R'_2, R'_5, and R'_6 stands for R_1, R_2, R_5, and R_6 respectively or any suitable FG (functional group) which may be transformed to R_1, R_2, R_5, and R_6

Scheme 3

Compounds according to the present invention may in special cases be prepared by a simple functional group interconversion (FGI), meaning a standard process, known to those skilled in the art of organic synthesis, where a functional group in compounds with the general formula I or I' is transformed into a different functional group in one or more synthetic steps, leading to a new compound with the general formula I. Examples of such processes include, but are not limited to, hydrolysis of an ester to give an acid under basic conditions, deprotection of a methylether to give a phenol by treatment with e.g. borontribromide (BBr_3), and catalytic hydrogenation of an olefin to give a saturated hydrocarbon. Non limiting examples of such transformations are described in "Comprehensive Organic Transformations", by R. C. Larock, VCH 1989, which is hereby incorporated as reference and in general procedures. Especially, the use of general protective groups in one or more synthetic steps may be convenient in the synthesis of compounds with the general formula I. Examples of such general protective groups include, but are not limited to, methyl, ethyl, *tert*-butyl or benzyl esters as protective groups of an hydroxy group; tetrahydropyranyl- or silyl-ethers as protective groups of an hydroxy group.

As shown in Scheme 2 and 3 each intermediate compound may be transformed by an FGI process as described above to give new compounds with the same general formula (e.g. an hydroxy group may be protected as an *tert*-butyl-dimethyl-silyl ether). This is only to illustrate the flexibility in the synthesis, and in general the described sequence of processes is only one of many possible strategies for the synthesis of compounds of the present invention. That is, it may be more advantageous in some cases to alter the sequence of the processes described above. The described sequence of processes is not considered as being

limiting the preparation of compounds of the present invention of general formula I, and alteration of the reaction sequence may be an obvious alternative for those skilled in the art of organic synthesis. This aspect of the invention may especially be advantageous in the synthesis of compounds with different substituents in the R_4, R_5, and R_6 groups. Readily available intermediates may serve as starting point for the synthesis of various series of compounds covered by the general formula I.

Pharmaceutical compositions

In another aspect, the invention relates to a pharmaceutical composition comprising, as an active component, a compound of formula I together with a pharmaceutically acceptable excipient, carrier or vehicle. Furthermore, the invention relates to the use of a compound of formula I for the preparation of a medicament for the prevention, treatment or amelioration of inflammatory diseases or conditions.

Pharmaceutical compositions of the invention may be in unit dosage form such as tablets, pills, capsules, powders, granules, elixirs, syrups, emulsions, ampoules, suppositories or parenteral solutions or suspensions; for oral, parenteral, opthalmic, transdermal, intra-articular, topical, pulmonal, nasal, buccal or rectal administration or in any other manner appropriate for the formulation of anti-inflammatory compounds and in accordance with accepted practices such as those disclosed in *Remington: The Science and Practice of Pharmacy*. 19th Ed., Mack Publishing Company, 1995. In the composition of the invention, the active component may be present in an amount of from about 0.1 to about 99% by weight of the composition.

For oral administration in the form of a tablet or capsule, a compound of formula I may suitably be combined with an oral, non-toxic, pharmaceutically acceptable carrier such as ethanol, glycerol, water or the like. Furthermore, suitable binders, lubricants, disintegrating agents, flavouring agents and colourants may be added to the mixture, as appropriate. Suitable binders include, e.g., lactose, glucose, starch, gelatin, acacia gum, tragacanth gum, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes or the like. Lubricants include, e.g., sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride or the like. Disintegrating agents include, e.g., starch, methyl cellulose, agar, bentonite, xanthan gum or the like.

For the preparation of solid compositions such as tablets, the active compound of formula I is mixed with one or more excipients, such as the ones described above, and other

pharmaceutical diluents such as water to make a solid preformulation composition containing a homogenous mixture of a compound of formula I. The term "homogenous" is understood to mean that the compound of formula I is dispersed evenly throughout the composition so that the composition may readily be subdivided into equally effective unit dosage forms such as tablets or capsules. The preformulation composition may then be subdivided into unit dosage forms containing from about 0.05 to about 1000 mg, in particular from about 0.1 to about 500 mg, of the active compound of the invention.

Liquid formulations for either oral or parenteral administration of the compound of the invention include, e.g., aqueous solutions, syrups, aqueous or oil suspensions and emulsion with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil. Suitable dispersing or suspending agents for aqueous suspensions include synthetic or natural gums such as tragacanth, alginate, acacia, dextran, sodium carboxymethylcellulose, gelatin, methylcellulose or polyvinylpyrolidone.

For parenteral administration, e.g. intramuscular, intraperitoneal, subcutaneous or intravenous injection or infusion, the pharmaceutical composition preferably comprises a compound of formula I dissolved or solubilised in an appropriate, pharmaceutically acceptable solvent. For parenteral administration, the composition of the invention may include a sterile aqueous or non-aqueous solvent, in particular water, isotonic saline, isotonic glucose solution, buffer solution or other solvent conventionally used for parenteral administration of therapeutically active substances. The composition may be sterilised by, for instance, filtration through a bacteria-retaining filter, addition of a sterilising agent to the composition, irradiation of the composition, or heating the composition. Alternatively, the compound of the invention may be provided as a sterile, solid preparation, e.g. a freeze-dried powder, which is dissolved in sterile solvent immediately prior to use.

The composition intended for parenteral administration may additionally comprise conventional additives such as stabilisers, buffers or preservatives, e.g. antioxidants such as methylhydroxybenzoate or the like.

Compositions for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.

Compositions suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or

biodegradable polymer systems may also be used to present the active ingredient for both intra-articular and ophthalmic administration.

Compositions suitable for topical administration, including eye treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. For topical administration, the compound of formula I may typically be present in an amount of from 1 to 20% by weight of the composition, but may also be present in an amount of up to about 50% of the composition.

Compositions suitable for administration to the nasal or buccal cavity or for inhalation include powder, self-propelling and spray formulations, such as aerosols and atomizers. Such compositions may comprise a compound of formula I in an amount of 0.1-20%, e.g. 2%, by weight of the composition.

The composition may additionally comprise one or more other active components conventionally used in the treatment of various inflammatory diseases and conditions. Examples of such additional active components may be selected from the group consisting of glucocorticoids, vitamin D and vitamin D analogues, antihistamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methylxanthines, β-adrenergic agents, COX-2 inhibitors, salicylates, infomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol lowering agents, retinoids, zinc salts and salicylazosulfapyridine.

In a further aspect, the invention relates to a method of treating inflammatory diseases or conditions, or cancer, the method comprising administering, to a patient in need thereof, an effective amount of a compound of formula I.

A suitable dosage of the compound of the invention will depend, inter alia, on the age and condition of the patient, the severity of the disease to be treated and other factors well known to the practising physician. The compound may be administered either orally or parenterally according to different dosing schedules, e.g. daily or with weekly intervals. In general a single dose will be in the range from 0.1 to 400 mg/kg body weight. The compound may be administered as a bolus (i.e. the entire daily dosis is administered at once) or in divided doses two or more times a day.

Inflammatory diseases or conditions contemplated for treatment with the present compounds are inflammatory diseases where modulation of cytokine expression and secretion may be mediated by MAP kinases such as the p38 MAP kinase as discussed above. Examples of inflammatory diseases or conditions believed to be mediated by the p38 MAP kinase are selected from the group consisting of asthma, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, inflammatory bowel diease, Crohn's disease, neurological inflammations, inflammatory eye diseases, proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis and acne vulgaris, uveitis, sepsis, septic shock and osteoporosis.

The treatment may additionally involve administration of one or more other anti-inflammatory active components such as glucocorticoids, vitamin D and vitamin D analogues, antihistamines, platelet activating factor (PAF) antagonists, anticholinergic agents, methylxanthines, β-adrenergic agents, COX-2 inhibitors, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol lowering agents, retinoids, zinc salts and salicylazosulfapyridine. The administration of a compound of the present invention and another anti-inflammatory component may be either concomitantly or sequentially.

Pharmacological methods

To study the effect of compounds of the present invention *in vitro*, the inhibition of IL-1β and TNF-α secretion was determined using the following procedure:

Cytokine production was measured in the media from lipopolysaccharide (LPS) stimulated peripheral blood mononuclear cells. The mononuclear cells were isolated from human peripheral blood by Lymphoprep® (Nycomed, Norway) fractionation and suspended in RPMI 1640 (growth medium) with foetal calf serum (FCS, 2%), at a concentration of 5×10^5 cells/ml. The cells were incubated in 24-well tissue culture plates in 1 ml aliquots. Test compounds were dissolved in dimethylsulfoxide (DMSO, 10 mM) and were diluted with the medium. Compounds were added to the cells for 30 minutes, then LPS (1 mg/ml final concentration) was added. The plates were incubated for 18 hours, and the concentration of IL-1β and TNF-α in the medium was determined by enzyme-linked immunosorbent assays. The median inhibitory concentrations (IC_{50}) of the compounds were calculated. The results are shown in Table 1.

Table 1. **Inhibition of cytokines production in vitro by compounds of the present invention.**

Compound No.	The median inhibition concentration (IC_{50}, nM) of IL-1β	TNF-α
Compound 104	2.0	1.3
Compound 106	2.0	1.0
Compound 107	3.2	3.2
Compound 109	4.0	3.2
Compound 112	4.0	0.6
Compound 114	2.5	0.4
Compound 115	1.3	0.3
Compound 116	1.0	1.0
Compound 117	4.0	1.0
Compound 118	2.2	2.0
Compound 119	1.3	0.4
Ref. comp. a	13	7.1
Ref. comp. b	6.3	6.3
Ref. comp. c	32	6.3
Ref. comp. d	7.9	3.2
Ref. comp. e	6.3	3.2

Table 1. **Inhibition of cytokines production in vitro by compounds of the present invention. The median inhibitory concentration (IC_{50}, nM) of**

Compound No.	IL-1β	TNF-α
Ref. comp. f	13	4.0

Ref. comp. a: (4-(2-aminophenylamino)-2-chloro-2'-methylbenzophenone, Compound 156 disclosed in WO 98/32730.

Ref. comp. b: 2'-[3-Chloro-4-(2-methylbenzoyl)phenylamino]octananilide, Compound 102 disclosed in WO 01/05746.

Ref. comp. c: 1-Acetoxymethyl *N*-[2-[3-chloro-4-(2-methylbenzoyl)phenylamino]phenyl]carbamate, Compound 109 disclosed in WO 01/05749.

Ref. comp. d: 1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)phenylamino]-5-fluoro-phenyl]urea, Compound 114 disclosed in WO 01/05751.

Ref. comp. e: 2,2,2-Trifluoro-*N*-[2-[3-chloro-4-(2-methylbenzoyl)phenylamino]-5-fluoro-phenyl]acetamide, Compound 102 disclosed in WO 01/05745.

Ref. comp. f: 2-Chloro-4-(3-fluoro-2-methyl-phenylamino)-2'-methylbenzophenone, Compound 131 disclosed in WO 01/42189.

These results show that compounds of the present invention are highly potent inhibitors of the production of IL-1β, TNF-α and show a surprisingly higher cytokine inhibitory activity than the reference compounds, thus making them potentially useful in the treatment of inflammatory diseases.

Furthermore, the novel aminobenzophenone derivatives have surprisingly favourable pharmacokinetic properties such as absorption and metabolic stability.

p38α MAP kinase assay

Cell culture

COS-1 cells (derived from African green monkey kidney fibroblast-like cell containing wild-type T antigen under control of the SV40 promotor) were obtained from ATCC (ATCC no. CRL-1650) and grown in growth medium (DMEM without phenolred, 10% FCS, 2 mM L-glutamine, 100U penicillin and 100 µg streptomycin/ml) at 37°C with 5% CO_2. The cells were passaged twice a week by trypsination (0.25% trypsin, 1 mM EDTA in PBS) and were

split 1:10. The medium was changed every second or third day. The cell line was regularly tested with the Mycoplasma PCR Primer Set (Stratagene) and found to be free of *Mycoplasma*. Tissue culture media, FCS, L-glutamine and penicilin and streptomycin are from Bribco BRL, Gaithersburg, MD, USA.

Transient expression of COS-1 cells

On day one COS-1 cells were seeded in 143 cm^2 petridish with a density of 2×10^4celler/cm^2 in growth medium. At day 2 the cells were co-transfected with 5 µg (total) of experimental plasmid DNA, expressing the FLAG-p38α and FLAG-MKK6(EE). The plasmids were introduced into the COS-1 cells in serum-free medium using DOTAP™ (Boehringer-Mannheim, Mannheim, Germany). Plasmid DNA was prepared and purified using the QIAGEN EndoToxin-free Maxiprep-500 kit (Hilden, Germany). Briefly, DNA and DOTAP™ were mixed for exactly 15 min. at 37°C in the CO_2 incubator. The transfection-mixture was hereafter transferred to a 15-ml falcon-tube and transfection-medium (DMEM with L-Glutamine and Pen./Strep. but without serum) was added to the transfection-mixture, followed by addition to the cell-monolayer. After 4 hours of incubation with DOTAP™ and plasmids, the medium containing double amount of serum was added to the cells bringing the final concentration of serum up to 10%. The cells were then incubated for 24 hours before kinase reaction.

Immunoprecipitation

After 24 hrs of incubation the reaction was stopped by putting the petri dish on an ice-bath. The medium was aspirated, and the cell monolayer was washed once in ice-cold PBS (137 mM NaCl, 1.5 mM KH_2PO_4, 2.7 mM KCl, 8.1 mM $Na_2HPO_4 \cdot 2H_2O$), and hereafter solubilised for 10 min. in 1.5 ml lysis buffer (50 mM HEPES, pH 7.5, 150 mM NaCl, 10 mM EDTA, 10 mM $Na_4P_2O_7$, 100 mM NaF, 2 mM Na_3VO_4 ,1% Triton-X-100, Pefabloc 500 µM, Leupeptin 10 µg/µl, Aprotinin 10 µg/µl) was added. The cell-monolayer was scraped by a rubber-policeman, and transferred to an Eppendorf tube. The solubilised cells were clarified by centrifugation at 10.000×g for 10 min. at 4°C. The supernatant was transferred to 50 µl prewashed Protein G Sepharose beads in HNT-buffer (30 mM HEPES, pH 7.5, 30 mM NaCl, 0.1% Triton X-100) and were incubated with 2 µg/sample of monoclonal anti-FLAG™ M2 antibody (raised against the FLAG-epitope, NH_2-Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys-COOH) for 1 hour at room temperature. The anti-FLAG M2 monoclonal antibody was obtained from Sigma (cat. no. F-3165). Approx. 60 µg protein of clarified cell lysate were added to the preadsorbed anti-FLAG™ antibodies on Protein G Sepharose beads and incubated for 90 min. at 4°C in a blood sample mixer. After the immunoprecipitation period the Sepharose

beads were washed twice in lysis buffer and twice in a kinase reaction buffer (25 mM HEPES pH 7.5, 10 mM magnesium acetate, 50μM ATP).

Incubation of the compounds with purified p38α kinase

The pre-washed immunoprecipitated anti-FLAG-p38 adsorbed on Protein G Sepharose beads was washed twice in 1×kinase-buffer (25 mM HEPES pH 7.5, 10 mM magnesium acetate, 50μM ATP), and the supernatant was aspirated. The compounds were diluted in 1× kinase buffer at the appropriate concentration. The compounds were added to the washed immunoprecipitated and activated FLAG-p38 adsorbed on the Protein G Sepharose beads for 30 min. at 30°C in a volume of 100 μl. Every 10 min. the Eppendorf tubes were tapped to ensure that the beads and the compounds were in the solution. After 30 min. incubation, the beads were spun down and the supernatant was aspirated.

p38α MAP Kinase Reaction

The kinase reaction was started by adding 1 μg GST-ATF-2 substrate (Santa Cruz, LaJolla, CA, USA, cat. no. sc-4114) together with 2 μCi γ-^{32}P-ATP in 1× kinase-buffer per sample. The reaction was allowed to proceed for 30 min. at 30°C, and it was stopped by adding 40 μl of 2×SDS-sample buffer to the kinase reaction. The samples were boiled, spinned down, and resolved on a 15% SDS-PAGE. The dried SDS-PAGE gel was exposed to a Phospho-Imager screen and the radioactive PHAS-1 bands were quantified by the STORM860 Phospho-Imager (Molecular Dynamics, Sunnyvale, CA, USA) using the ImageQuaNT software.

In this assay, Compound 112 was found to be a potent p38 MAP kinase inhibitor with an IC_{50} of 2 nM.

The invention is described in further detail in the following examples which are not in any way intended to limit the scope of the invention as claimed.

EXAMPLES

General procedures

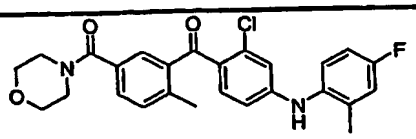
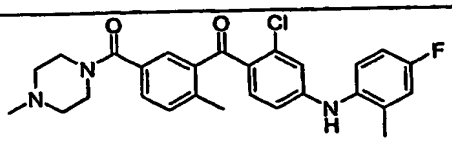
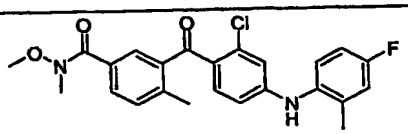
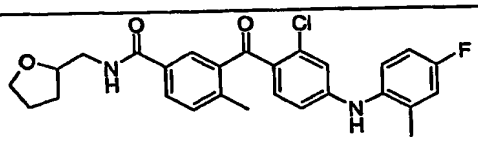
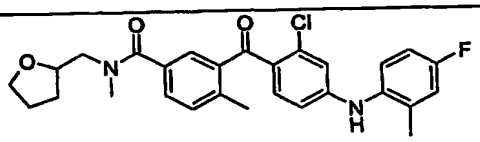
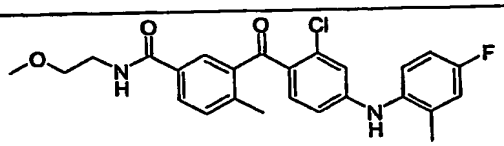
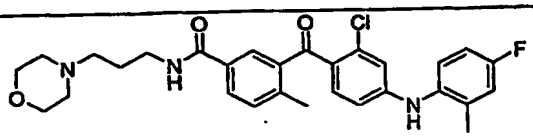
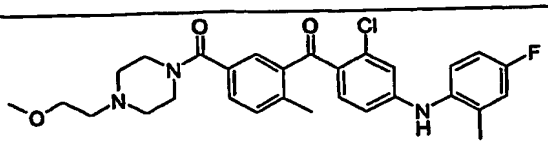
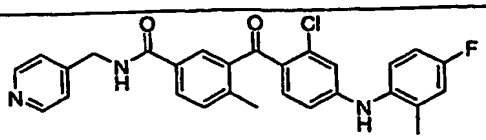
All melting points are uncorrected. For ^{1}H nuclear magnetic resonance (NMR) spectra (300 MHz) and ^{13}C NMR (75.6 MHz) chemical shift values (δ) (in ppm) are quoted, unless otherwise specified; for deuteriochloroform solutions relative to internal tetramethylsilane (δ = 0.00) or chloroform (δ = 7.26) or deuteriochloroform (δ = 76.81 for ^{13}C NMR) standard. The value of a multiplet, either defined (doublet (d), triplet (t), quartet (q)) or not (m) at the approximate mid point is given unless a range is quoted. All organic solvents used were

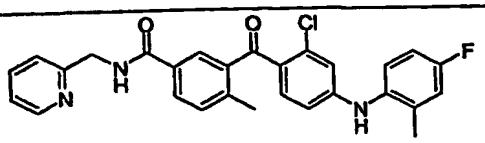
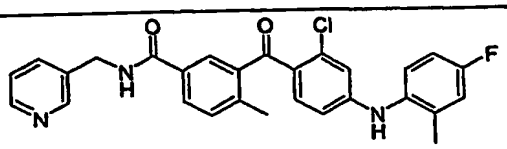
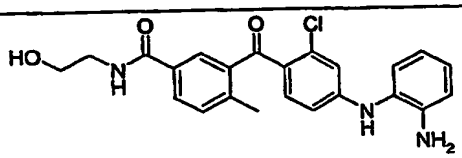
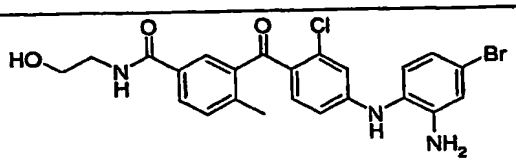
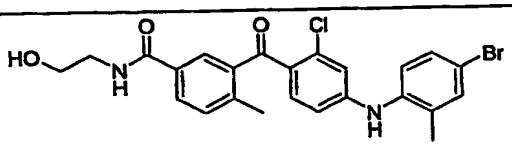
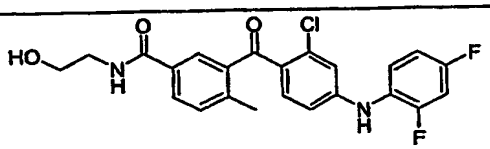
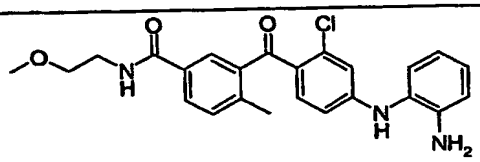
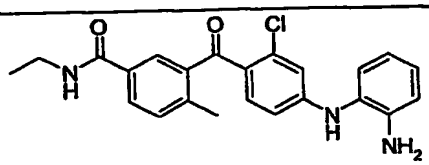
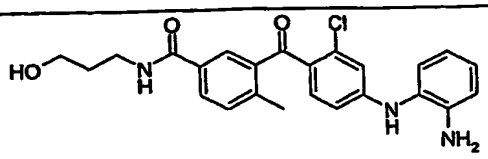
anhydrous. Chromatography was performed on silica gel using the flash technique. Appropriate mixtures of ethyl acetate, dichloromethane, methanol, and petroleum ether (40-60) were used as eluents unless otherwise noted.

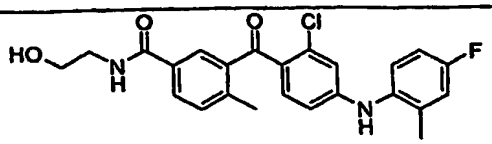
The following abbreviations have been used:

aq	aqueous
dba	Dibenzylideneacetone
DCM	Dichloromethane
DMF	*N,N*-Dimethylformamide
DIEA	Ethyl diisopropyl amine
EtOAc	Ethyl acetate
FDPP	Diphenyl-phosphinic acid pentafluorophenyl ester
h	hour(s)
NMP	*N*-methylmorpholine
NMR	Nuclear magnetic resonance
rac-BINAP	Racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl
RT	Room temperature
THF	Tetrahydrofuran
THP	Tetrahydropyran
v	volume

Table 2. Exemplified compounds of general formula I

Compound	Example no.	Structure
101	1	
102	2	
103	3	
104	4	
105	5	
106	6	
107	7	
108	8	
109	9	

110	10	
111	11	
112	12	
113	13	
114	14	
115	15	
116	16	
117	17	
118	18	

119	19	

Preparation 1:

3-(2-Chloro-4-nitrobenzoyl)-4-methylbenzoic acid methyl ester (Compound 401)

A dry flask was charged with 3-iodo-4-methylbenzoic acid methyl ester (21.6 g, 78.2 mmol) and the flask was evaporated and then filled with argon and this process repeated twice. Dry THF (140 mL) was added, and the solution cooled to -50 °C; then isopropylmagnesium chloride (41 mL, 2.0 M in diethyl ether, 82 mmol) was added slowly over 15 min keeping the temperature below -40 °C. On completion of the addition the reaction mixture was stirred at -40 °C for 45 min. A THF solution of $ZnCl_2$ (10.78 g, 79.1 mmol, 0.8 M) was added dropwise over 20 min. The reaction mixture was stirred at 0 °C for 65 min; then 2-chloro-4-nitro-benzoyl chloride (17.2 g, 78.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (4.03 g, 3.49 mmol) were added and the reaction mixture was allowed to warm to room temperature. After 4 h the reaction mixture was poured into a mixture of toluene/EtOAc/water, then shaken and separated. The aqueous phase was extracted with two more portions of EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude product. Crystallization from mixtures of EtOAc/petroleum ether (40-60) gave the title compound as yellow solid. The mother liquid was concentrated in vacuo and purified by chromatography using DCM as the eluent to give a second crop of the title compound.

Preparation 2:

3-(4-Amino-2-chlorobenzoyl)-4-methylbenzoic acid methyl ester (Compound 402)

A solution of compound 401 (7.83 g, 23.5 mmol) in methanol (100 mL) was added zinc dust (15.3 g, 235 mmol) and ammonium chloride (6.27 g, 117 mmol) in one portion under stirring. A $CaCl_2$ tube was mounted on the flask and the flask was placed in an oil bath with a temperature of 90 °C. After 2 h the reaction mixture was cooled to RT, filtered, and then poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried (MgSO4), filtered, and concentrated *in vacuo* to afford the crude product. Crystallization from a mixture of EtOAc/petroleum ether (40-60) (2:3) gave the title compound as light yellow solid.

Preparation 3:

3-(4-Amino-2-chlorobenzoyl)-4-methylbenzoic acid (Compound 403)

A solution of compound 402 (1.61 g, 5.3 mmol) in ethanol (50 mL) was added a solution of sodium hydroxide (2 M, 30 mL) and then stirred under reflux for 90 min. The reaction mixture was made weakly acidic (pH = 5) by slowly addition of hydrochloric acid (4N), and then poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title compound as orange solid. It was used without any further purification.

Preparation 4:

(4-Amino-2-chlorophenyl)-[2-methyl-5-(morpholine-4-carbonyl)phenyl]-methanone (Compound 404)

A solution of compound 403 (150 mg, 0.47 mmol) in DMF (2.00 mL) in a reaction vial (8 mL) was added morpholine (41 µL, 0.47 mmol), FDPP (253 mg, 0.66 mmol) and DIEA (402 µL, 2.35 mmol). The vial was flushed with argon, closed, and then shaken at RT for 24 h. The reaction mixture was concentrated in vacuo at 40 °C and then purified by chromatography using EtOAc/petroleum ether (40-60) 4:1 followed by EtOAc as the eluent to give the title compound as orange syrup.

Example 1:

[2-Chloro-4-(4-fluoro-2-methylphenylamino)phenyl]-[2-methyl-5-(morpholine-4-carbonyl)phenyl]-methanone (Compound 101)

2-Bromo-5-fluorotoluene (47 µL, 0.37 mmol) was dissolved in 3 mL dry 1,4-dioxane in a vial under an argon atmosphere. Compound 404 (110 mg, 0,31 mmol) was added and dissolved in the solvent. Rac-BINAP (7.3 mg, 0.012 mmol), $Pd_2(dba)_3$ (7.0 mg, 0.008 mmol) and Cs_2CO_3 (141 mg, 0.43 mmol) were added, and the reaction mixture was stirred under an argon atmosphere at 100 °C for 72 h. The reaction mixture was filtered and then purified by continuous gradient flash chromatography using EtOAc/petroleum ether (40-60) (v:v= 0:100 to 50:50) as the eluent to afford the title compound as brown oil. ^{13}C NMR ($CDCl_3$) δ 195.4, 169.7, 160.6, 150.3, 139.8, 139.7, 136.6, 135.4, 134.0, 133.7, 132.4, 131.5, 129.2, 127.9, 127.4, 127.0, 117.8, 115.0, 113.8, 111.7, 66.8, 48.3, 42.8, 20.2, 18.1.

Preparation 5:

(4-Amino-2-chlorophenyl)-[2-methyl-5-(4-methylpiperazine-1-carbonyl)phenyl]-methanone (Compound 405)

The reaction was carried out as described in the preparation of compound 404, using *N*-methylpiperazine (52 µL, 0.47 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as brown syrup.

Example 2:
[2-Chloro-4-(4-fluoro-2-methylphenylamino)phenyl]-[2-methyl-5-(4-methyl-piperazine-1-carbonyl)phenyl]-methanone (Compound 102)

The reaction was carried out as described in the preparation of compound 101, using compound 405 (143 mg, 0.45 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow foam. ^{13}C NMR ($CDCl_3$) δ 195.5, 169.6, 160.6, 150.1, 139.6, 139.5, 136.5, 135.5, 134.0, 133.7, 133.0, 131.4, 129.2, 128.0, 127.4, 127.4, 117.9, 115.0, 113.9, 111.7, 54.8, 47.8, 46.0, 42.1, 20.2, 18.1.

Preparation 6:
3-(4-Amino-2-chlorobenzoyl)-*N*-methoxy-4,*N*-dimethylbenzamide (Compound 406)

The reaction was carried out as described in the preparation of compound 404, using the salt *N,O*-dimethylhydroxylamine hydrochloride (46 mg, 0.47 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as orange solid.

Example 3:
3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-*N*-methoxy-4,*N*-dimethylbenzamide (Compound 103)

The reaction was carried out as described in the preparation of compound 101, using compound 406 (125 mg, 0.38 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow foam. ^{13}C NMR ($CDCl_3$) δ 195.6, 168.9, 160.6, 150.0, 140.7, 139.2, 136.5, 135.5, 133.9, 133.8, 131.1, 131.0, 130.5, 129.5, 127.7, 127.3, 117.9, 115.1, 113.9, 111.7, 65.9, 61.1, 20.4, 15.3.

Preparation 7:
3-(4-Amino-2-chlorobenzoyl)-4-methyl-*N*-(tetrahydrofuran-2-ylmethyl)benzamide (Compound 407)

The reaction was carried out as described in the preparation of compound 404, using (tetrahydrofuran-2-yl)methylamine (31 mg, 0.31 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow oil.

Example 4:
3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-(tetrahydrofuran-2-ylmethyl)benzamide (Compound 104)

The reaction was carried out as described in the preparation of compound 101, using compound 407 (85 mg, 0.23 mmol) as the amine. Purification was done by flash

chromatography to afford the title compound as yellow foam. ^{13}C NMR ($CDCl_3$) δ 195.5, 166.8, 160.6, 150.3, 141.1, 140.1, 136.6, 135.7, 134.2, 133.8, 131.8, 131.4, 128.6, 127.6, 127.4, 127.0, 117.8, 115.2, 113.8, 111.6, 77.6, 68.2, 43.7, 28.7, 25.9, 20.2, 18.1.

Preparation 8:
3-(4-Amino-2-chlorobenzoyl)-4,*N*-dimethyl-*N*-(tetrahydrofuran-2-ylmethyl)benzamide (Compound 408)
The reaction was carried out as described in the preparation of compound 404, using methyl(tetrahydrofuran-2-ylmethyl)amine (36 mg, 0.31 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow oil.

Example 5:
3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4,*N*-dimethyl-*N*-(tetrahydrofuran-2-ylmethyl)benzamide (Compound 105)
The reaction was carried out as described in the preparation of compound 101, using compound 408 (85 mg, 0.23 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as brown syrup. ^1H NMR ($CDCl_3$) δ 7.41 – 7.24 (m,4H), 7.15 (dd,1H), 6.97 (dd,1H), 6.90 (dt,1H), 6.61 (d,1H), 6.48 (dd,1H), 6.23 (bs,1H), 4.17 – 3.0 (m,8H), 2.41 (s,3H), 2.21 (s,3H), 2.0 – 1.45 (m,4H).

Preparation 9:
3-(4-Amino-2-chlorobenzoyl)-*N*-(2-methoxyethyl)-4-methylbenzamide (Compound 409)
The reaction was carried out as described in the preparation of compound 404, using 2-methoxyethylamine (23 mg, 0.31 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow oil.

Example 6:
3-[2-Chloro-4-(4-fluoro-2-methyl-phenylamino)benzoyl]-*N*-(2-methoxyethyl)-4-methylbenzamide (Compound 106)
The reaction was carried out as described in the preparation of compound 101, using compound 409 (60 mg, 0.17 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as syrup. ^{13}C NMR ($CDCl_3$) δ 195.6, 166.9, 160.7, 150.2, 141.2, 140.1, 136.5, 135.7, 134.2, 133.6, 131.7, 131.4, 128.7, 127.6, 127.3, 127.3, 117.8, 115.2, 113.9, 111.7, 71.1, 58.9, 39.8, 20.3, 18.1.

Preparation 10:

3-(4-Amino-2-chlorobenzoyl)-4-methyl-*N*-(3-morpholin-4-ylpropyl)benzamide (Compound 410)

The reaction was carried out as described in the preparation of compound 404, using 3-morpholin-4-yl-propylamine (45 mg, 0.31 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as foam.

Example 7:

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-(3-morpholin-4-yl-propyl)benzamide (Compound 107)

The reaction was carried out as described in the preparation of compound 101, using compound 410 (37 mg, 0.09 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as brown oil. ^{13}C NMR ($CDCl_3$) δ 195.6, 166.6, 160.6, 150.3, 140.8, 140.3, 136.5, 135.7, 133.7, 133.7, 131.3, 128.6, 127.3, 127.3, 117.8, 115.2, 113.9, 111.7, 66.9, 58.7, 53.9, 40.6, 24.2, 20.2, 18.1.

Preparation 11:

(4-Amino-2-chlorophenyl)-{5-[4-(2-methoxyethyl)piperazine-1-carbonyl]-2-methylphenyl}-methanone (Compound 411)

The reaction was carried out as described in the preparation of compound 404, using 1-(2-methoxyethyl)piperazine (45 mg, 0.31 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as foam.

Example 8:

[2-Chloro-4-(4-fluoro-2-methylphenylamino)phenyl]-{5-[4-(2-methoxyethyl)piperazine-1-carbonyl]-2-methylphenyl}-methanone (Compound 108)

The reaction was carried out as described in the preparation of compound 101, using compound 411 (90 mg, 0.22 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow oil. ^{13}C NMR ($CDCl_3$) δ 195.5, 169.5, 160.6, 150.3, 139.6, 139.4, 136.5, 135.4, 134.0, 133.8, 132.9, 131.4, 129.1, 127.9, 127.3, 127.0, 117.8, 115.0, 113.8, 111.6, 70.0, 58.9, 57.8, 53.8, 53.2, 47.7, 42.1, 20.2, 18.1.

Preparation 12:

3-(4-Amino-2-chlorobenzoyl)-4-methyl-*N*-pyridin-4-ylmethylbenzamide (Compound 412)

The reaction was carried out as described in the preparation of compound 404, using C-pyridin-4-yl-methylamine (31 µL, 0.31 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow solid.

Example 9:
3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-pyridin-4-ylmethylbenzamide (Compound 109)
The reaction was carried out as described in the preparation of compound 101, using compound 412 (100 mg, 0.26 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow solid. ^{13}C NMR (DMSO-d_6) δ 194.3, 165.5, 159.5, 151.0, 149.4, 148.4, 139.7, 136.2, 134.3, 134.1, 131.2, 131.1, 131.0, 128.9, 127.1, 127.0, 124.9, 122.1, 117.4, 114.1, 113.5, 111.0, 41.7, 19.5, 17.6.

Preparation 13:
3-(4-Amino-2-chlorobenzoyl)-4-methyl-*N*-pyridin-2-ylmethylbenzamide (Compound 413)
The reaction was carried out as described in the preparation of compound 404, using C-pyridin-2-yl-methylamine (31 µL, 0.31 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow solid.

Example 10:
3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-pyridin-2-ylmethylbenzamide (Compound 110)
The reaction was carried out as described in the preparation of compound 101, using compound 413 (79 mg, 0.21 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow solid. ^{13}C NMR (DMSO-d_6) δ 194.3, 165.3, 159.5, 151.0, 148.8, 148.0, 139.7, 139.6, 136.2, 135.1, 134.9, 134.3, 134.1, 131.2, 131.0, 128.9, 127.1, 127.0, 124.9, 123.4, 117.4, 114.1, 113.4, 111.0, 40.3, 19.5, 17.6.

Preparation 14:
3-(4-Amino-2-chlorobenzoyl)-4-methyl-*N*-pyridin-3-ylmethylbenzamide (Compound 414)
The reaction was carried out as described in the preparation of compound 404, using C-pyridin-3-yl-methylamine (31 µL, 0.31 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as yellow foam.

Example 11:
3-[2-Chloro-4-(4-fluoro-2-methyl-phenylamino)-benzoyl]-4-methyl-N-pyridin-3-ylmethyl-benzamide (Compound 111)
The reaction was carried out as described in the preparation of compound 101, using compound 414 (90 mg, 0.24 mmol) as the amine. Purification was done by flash chromatography to afford the title compound as solid. ^{13}C NMR (DMSO-d_6) δ 194.4, 165.3,

159.4, 157.8, 150.9, 148.7, 139.7, 136.6, 136.2, 134.3, 134.2, 134.1, 131.3, 131.0, 128.9, 127.1, 127.0, 125.0, 122.0, 120.9, 117.4, 114.1, 113.4, 111.0, 44.6, 19.5, 17.6.

Preparation 15:

3-[2-Chloro-4-(2-nitrophenylamino)benzoyl]-4-methylbenzoic acid methyl ester (Compound 415)

A Schlenk tube was charged with compound 402 (4.00 g, 13.1 mmol) in 1,4-dioxane (40 mL), 1-iodo-2-nitro-benzene (3.91 g, 15.7 mmol), Cs_2CO_3 (5.98 g, 18.3 mmol), $Pd_2(dba)_3$ (302 mg, 0.33 mmol), and rac-BINAP (308 mg, 0.49 mmol). The tube was capped with a rubber septum, flushed with argon for 5 min, and then stirred at 100 °C for 2 h. The reaction mixture was allowed to cool to room temperature, and then poured into a mixture of water and EtOAc. The aqueous phase was extracted twice with more EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by chromatography eluting with petroleum ether (40-60)/EtOAc 4:1 to afford the title compound as yellow solid.

Example 16:

3-[2-Chloro-4-(2-nitrophenylamino)benzoyl]-4-methylbenzoic acid (Compound 416)

To a suspension of compound 415 (3.00 g, 7.06 mmol) in methanol (20 mL) was added water (4.0 mL) followed by lithium hydroxide (845 mg, 35 mmol). The mixture was then stirred at reflux for 30 min. The reaction mixture was made acidic (pH = 5) by slowly addition of H_2SO_4 (1N), and then poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was triturated in EtOAc/pentane 1:1 (20 mL) to afford the title compound as yellow solid.

Preparation 17:

3-[2-Chloro-4-(2-nitrophenylamino)benzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 417)

To a solution of compound 416 (2.42 g, 5.90 mmol) in DMF (20 mL) was added 2-amino-ethanol (541 mg, 8.85 mmol), FDPP (2.72 g, 7.08 mmol), and DIEA (5 mL, 30 mmol) at 0 °C. The flask was flushed with argon and the temperature was allowed to come to RT. The reaction mixture was stirred at RT for 5 h, and then poured into a mixture of water (100 mL), H_2SO_4 (1N, 40 mL), and EtOAc (100 mL). The phases were separated and the aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by chromatography eluting with DCM/methanol 100:2 to afford the title compound as orange solid.

Example 18:
3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 112)

To a solution of compound 417 (2.21 g, 4.87 mmol) in methanol (40 mL) was added zinc dust (3.18 g, 48.7 mmol) and ammonium chloride (1.30 g, 24.3 mmol) in one portion under stirring. A $CaCl_2$ tube was mounted on the flask and the flask was placed in an oil bath with a temperature of 90 °C. After 1 h the reaction mixture was cooled to RT, filtered, and then poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product. The crude product was purified by chromatography eluting with DCM/methanol 100:5 (v:v) followed by 100:7 (v:v) to afford the title compound as yellow foam. ^{13}C NMR ($CDCl_3$) δ 195.7, 167.8, 150.3, 142.8, 141.2, 140.1, 135.6, 134.2, 131.4, 128.9, 127.8, 127.4, 127.0, 126.8, 125.0, 119.2, 116.5, 115.4, 111.9, 62.1, 42.9, 20.2.

Preparation 18:
3-[4-(4-Bromo-2-nitrophenylamino)-2-chlorobenzoyl]-4-methylbenzoic acid methyl ester (Compound 418)

A solution of compound 402 (1.00 g, 3.29 mmol) and 4-bromo-1-fluoro-2-nitrobenzene (0.4 mL, 3.29 mmol) in DMSO (7.0 mL) was slowly added potassium *tert*-butoxide (816 mg, 7.27 mmol) under stirring. After 4 h at RT the reaction mixture was poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product. The crude product was purified by chromatography eluting with petroleum ether (40-60)/EtOAc 9:1 to afford the title compound as orange solid.

Preparation 19:
3-[4-(4-Bromo-2-nitrophenylamino)-2-chlorobenzoyl]-4-methylbenzoic acid (Compound 419)

To a suspension of compound 419 (540 mg, 1.07 mmol) in methanol (5 mL) was added water (0.5 mL) and lithium hydroxide (128 mg, 5.35 mmol). The mixture was then stirred at reflux for 3 h. The reaction mixture was made acidic (pH = 2) by slowly addition of HCl (aq.) (1N), and then poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the title product as orange solid. It was used without any further purification.

Preparation 20:

3-[4-(4-Bromo-2-nitrophenylamino)-2-chlorobenzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 420)

The reaction was carried out as described in the preparation of compound 404, using 2-aminoethanol (56 µL, 0.94 mmol) as the amine and compound 419 (461 mg, 0.94 mmol) as the carboxylic acid. Purification was done by flash chromatography to afford the title compound as orange solid.

Example 13:

3-[4-(2-Amino-4-bromophenylamino)-2-chlorobenzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 113)

The reaction was carried out as described in the preparation of compound 112, using compound 420 (280 mg, 0.53 mmol) as the nitro compound. Purification was done by flash chromatography to afford the title compound as a solid. ^{13}C NMR (CD_3OD) δ 197.7, 169.5, 152.8, 147.0, 142.0, 141.8, 136.7, 135.4, 133.1, 132.4, 130.2, 129.4, 128.6, 127.2, 125.4, 121.3, 121.3, 119.4, 116.2, 112.7, 61.6, 43.6, 20.2.

Preparation 21:

3-[4-(4-Bromo-2-methylphenylamino)-2-chlorobenzoyl]-4-methylbenzoic acid methyl ester (Compound 421)

A reaction vial was charged with compound 402 (100 mg, 0.33 mmol) in 1,4-dioxane (1.0 mL), 4-bromo-1-iodo-2-methylbenzene (56 µL, 0.38 mmol), Cs_2CO_3 (15 mg, 0.46 mmol), $Pd_2(dba)_3$ (7.5 mg, 0.008 mmol), and rac-BINAP (7.7 mg, 0.012 mmol). The tube was flushed with argon for 5 min, closed and then stirred at 150 °C for 1 h in a microwave oven. The reaction mixture was allowed to cool to room temperature, and then poured into EtOAc. Filtration and concentration *in vacuo* gave the crude product. The crude product was purified by continuous gradient flash chromatography using EtOAc/petroleum ether (40-60) (v:v = 10:90 to 30:70) as the eluent to afford the title compound as orange solid.

Preparation 22:

3-[4-(4-Bromo-2-methylphenylamino)-2-chlorobenzoyl]-4-methylbenzoic acid (Compound 422)

The reaction was carried out as described in the preparation of compound 419, using compound 421 (525 mg, 1.11 mmol) as the ester. Purification was done by flash chromatography to afford the title compound as orange solid. It was used without any further purification.

Example 14:
3-[4-(4-Bromo-2-methylphenylamino)-2-chlorobenzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 114)

The reaction was carried out as described in the preparation of compound 404, using 2-aminoethanol (58 µL, 0.97 mmol) as the amine and compound 422 (431 mg, 0.97 mmol) as the carboxylic acid. Purification was done by flash chromatography to afford the title compound as yellow solid.

^{13}C NMR (DMSO-d_6) δ 194.6, 165.2, 149.8, 139.4, 139.4, 137.8, 135.1, 134.1, 133.9, 133.5, 131.7, 130.9, 129.5, 128.9, 127.0, 125.7, 125.5, 116.6, 115.0, 111.8, 59.6, 42.1, 19.5, 17.4

Preparation 23:
3-[2-Chloro-4-(2,4-difluorophenylamino)benzoyl]-4-methylbenzoic acid methyl ester (Compound 423)

A reaction vial was charged with compound 402 (750 mg, 2.47 mmol) in toluene (7.5 mL), 1-bromo-2,4-difluorobenzene (0.33 mL, 2.96 mmol), Cs_2CO_3 (1.13 g, 3.46 mmol), $Pd_2(dba)_3$ (114 mg, 0.12 mmol), and rac-BINAP (116 g, 0.18 mmol). The tube was flushed with argon for 5 min, closed and then warmed slowly to 200 °C. The reaction vial was shaken at 200 °C for 4 h. The reaction mixture was allowed to cool to room temperature, and then poured into EtOAc. Filtration and concentration *in vacuo* gave the crude product. The crude product was purified by continuous gradient flash chromatography using EtOAc/petroleum ether (40-60) (v:v = 2:98 to 20:80) as the eluent to afford the title compound as brown syrup.

Preparation 24:
3-[2-Chloro-4-(2,4-difluorophenylamino)benzoyl]-4-methylbenzoic acid (Compound 424)

The reaction was carried out as described in the preparation of compound 419, using compound 421 (360 mg, 0.87 mmol) as the ester. Purification was done by flash chromatography to afford the title compound as orange solid.

Preparation 25:
2-Methylacrylic acid 2-{3-[2-chloro-4-(2,4-difluorophenylamino)benzoyl]-4-methylbenzoylamino}ethyl ester (Compound 425)

The reaction was carried out as described in the preparation of compound 404, using 2-methylacrylic acid 2-aminoethyl ester (54 mg, 0.33 mmol) as the amine and compound 424 (120 mg, 0.30 mmol) as the carboxylic acid. Purification was done by flash chromatography to afford the title compound as orange foam.

Example 15:
3-[2-Chloro-4-(2,4-difluorophenylamino)benzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 115)

To a suspension of compound 425 (95 mg, 0.19 mmol) in methanol (1.0 mL) was added water (0.1 mL) and lithium hydroxide (23 mg, 0.95 mmol). The mixture was then stirred at reflux for 45 min. The reaction mixture was made acidic (pH = 2) by slowly addition of HCl (aq.) (1N), and then poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using EtOAc/petroleum ether (40-60) (v:v = 4:1 and 6:1) as the eluent to afford the title compound as yellow oil. ^{13}C NMR ($CDCl_3$) δ 195.6, 167.7, 159.4, 155.7, 148.3, 141.5, 139.8, 135.4, 133.8, 131.6, 131.5, 129.0, 128.6, 127.7, 124.6, 124.2, 116.2, 112.8, 111.7, 105.0, 62.3, 42.9, 20.3.

Preparation 26:
3-[2-Chloro-4-(2-nitrophenylamino)benzoyl]-*N*-(2-methoxyethyl)-4-methylbenzamide (Compound 426)

To a solution of compound 409 (85 mg, 0.25 mmol) and 1-fluoro-2-nitrobenzene (26 μL, 0.25 mmol) in DMSO (2.0 mL) was added potassium *tert*-butoxide (62 mg, 0.55 mmol) under stirring. After 2.5 h at RT the reaction mixture was poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product. The crude product was purified by chromatography eluting with DCM/EtOAc 4:1 to afford the title compound as orange oil.

Example 16:
3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-(2-methoxyethyl)-4-methylbenzamide (Compound 116)

The reaction was carried out as described in the preparation of compound 112, using compound 426 (72 mg, 0.15 mmol) as the nitro compound. Purification was done by flash chromatography to afford the title compound as yellow foam. ^{13}C NMR (DMSO-d_6) δ 194.4, 165.2, 151.2, 144.0, 139.9, 139.2, 134.1, 134.0, 131.5, 130.8, 128.7, 126.8, 126.6, 126.2, 124.4, 123.9, 116.3, 115.4, 114.2, 111.2, 70.3, 59.6, 57.8, 19.4.

Preparation 27:

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-4-methylbenzoic acid methyl ester (Compound 427)

The reaction was carried out as described in the preparation of compound 112, using compound 415 (1.8 g, 4.38 mmol) as the nitro compound. Purification was done by flash chromatography to afford the title compound as yellow syrup.

Preparation 28:

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-4-methylbenzoic acid (Compound 428)

To a solution of compound 427 (735 mg, 1.86 mmol) in ethanol (10 mL) was added a solution of sodium hydroxide (2 M, 10 mL). The mixture was then stirred under reflux for 2 h. The reaction mixture was made weakly acidic (pH = 5) by slowly addition of glacial acetic acid (5.0 mL), and then poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by continuous gradient flash chromatography using DCM/methanol (v:v = 90:10 to 85:15) as the eluent to afford the title compound as yellow syrup.

Example 17:

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-ethyl-4-methylbenzamide (Compound 117)

The reaction was carried out as described in the preparation of compound 404, using ethylamine hydrochloride (11 mg, 0.14 mmol) as the amine and compound 428 (54 mg, 0.14 mmol) as the carboxylic acid. Purification was done by flash chromatography to afford the title compound as yellow oil. ^{13}C NMR ($CDCl_3$) δ 195.7, 166.8, 162.6, 150.4, 142.9, 140.8, 140.1, 135.6, 134.2, 132.0, 131.3, 128.7, 127.6, 127.3, 127.0, 126.7, 125.1, 118.9, 116.4, 115.4, 111.8, 35.0, 20.2, 14.8.

Example 18:

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-(3-hydroxypropyl)-4-methylbenzamide (Compound 118)

The reaction was carried out as described in the preparation of compound 404, using 3-aminopropane-1-ol (11 µL, 0.14 mmol) as the amine and compound 428 (54 mg, 0.14 mmol) as the carboxylic acid. Purification was done by flash chromatography to afford the title compound as yellow oil. ^{13}C NMR ($CDCl_3$) δ 195.8, 167.7, 150.4, 142.9, 141.1, 140.1, 135.6, 134.2, 131.5, 131.4, 128.8, 127.7, 127.4, 127.0, 126.6, 125.1, 119.1, 116.5, 115.4, 111.8, 60.0, 37.4, 31.8, 20.2.

Preparation 29:

3-(4-Amino-2-chlorobenzoyl)-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 429)

The reaction was carried out as described in the preparation of compound 404, using 2-aminoethanol (190 µL, 3.13 mmol) as the amine and compound 403 (1.00 g, 3.13 mmol) as the carboxylic acid. Purification was done by flash chromatography to afford the title compound as yellow solid.

Preparation 30:

3-(4-Amino-2-chlorobenzoyl)-*N*-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-4-methylbenzamide (Compound 430)

A solution of compound 429 (490 mg, 1.47 mmol), 1,5-diazabicyclo(5.4.0)undecen-5-ene (0.9 mL, 5.88 mmol) and *tert*-butylchlorodimethylsilane (777 mg, 5.15 mmol) in acetonitrile (2.0 mL) was stirred for 2 h under an atmosphere of argon. The reaction mixture was poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a syrup. The syrup was stirred in a mixture of ethanol (5.0 mL) and glacial acetic acid (0.5 mL) for 18 h and then poured into a mixture of EtOAc/water. The aqueous phase was extracted with more EtOAc. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product. The crude product was purified by chromatography eluting with DCM/EtOAc (v:v = 4:1) to afford the title compound as yellow foam.

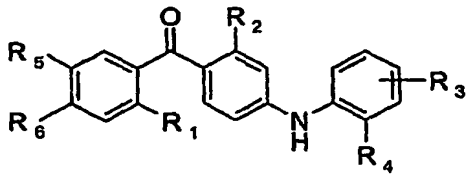
Example 19:

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 119)

2-Bromo-5-fluorotoluene (8 µL, 0.11 mmol) was dissolved in 1 mL dry 1,4-dioxane in a vial under an argon atmosphere. Compound 430 (42 mg, 0.09 mmol) was added and dissolved in the solvent. Rac-BINAP (2.1 mg, 0.003 mmol), $Pd_2(dba)_3$ (2.0 mg, 0.002 mmol) and Cs_2CO_3 (41 mg, 0.13 mmol) were added, and the reaction mixture was stirred under an argon atmosphere at 100 °C for 72 h. The reaction mixture was filtered and then dissolved in THF (1.00 mL). Tetrabutylammonium fluoride trihydrate (37 mg, 0.12 mmol) was added to the solution and the mixture was stirred at 60 °C for 45 min. The reaction mixture was poured into a mixture of EtOAc/water. The organic phase was washed with Na_2CO_3 (aq.), water, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude product. The crude product was purified by chromatography eluting EtOAc to afford the title compound as yellow/brown oil. ^{13}C NMR ($CDCl_3$) δ 195.6, 167.8, 160.6, 150.4, 141.2, 140.2, 136.5, 135.7, 134.3, 133.6, 131.5, 131.4, 128.8, 127.4, 127.4, 126.9, 117.8, 115.2, 113.9, 111.7, 77.2, 62.2, 42.9, 20.2, 18.1.

CLAIMS

1. A compound of general formula I



I

R_1 is halogen, hydroxy, mercapto, trifluoromethyl, amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4} alkylthio, C_{1-6}alkylamino, C_{1-4}alkoxycarbonyl, cyano, $-CONH_2$ or nitro;

R_2 is halogen, hydroxy, mercapto, trifluoromethyl, amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-6}alkylamino, C_{1-4}alkoxycarbonyl, cyano, $-CONH_2$, phenyl or nitro;

R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, cyano, carboxy, $CONH_2$, nitro, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-4} alkoxycarbonyl;

R_4 is hydrogen, halogen, R_8 or Y_1R_8;

Y_1 is -O-, -S-, -S(O)-, $-S(O)_2$-, $-NR_a$-, $-NR_aC(O)NR_b$-, $-NR_aC(O)$-, $-C(O)NR_a$-, $-C(O)NR_aO$-, -C(O)-, -C(O)O-, $-NR_aC(O)O$-, $-S(O)_2NR_a$-, $-NR_aS(O)_2$-;

R_a and R_b are the same or different, each representing hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-8}carbocyclyl, heterocyclyl or aryl;

R_8 is hydrogen, C_{1-10}alkyl-heterocyclyl, C_{1-10}alkyl-C_{3-12}carbocyclyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10} alkynyl, C_{3-12}carbocyclyl or heterocyclyl; each being optionally substituted by one or more, same or different substituents represented by R_7;

R_7 is halogen, hydroxy, mercapto, trifluoromethyl, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-6} alkylamino, C_{1-4}alkoxycarbonyl, C_{1-9} trialkylammonium in association with an anion, cyano, azido, nitro, -COOH, $-CONH_2$, -CONHR' or -CONRR', wherein R and R' are same or different, each representing hydrogen or C_{1-3}alkyl;

one of R_5 and R_6 is Y_2R_9, C_{1-6}alkyl-Y_2R_9, C_{1-6}alkenyl-Y_2R_9, C_{1-10}alkyl-heterocyclyl, C_{1-10}alkyl-C_{3-12}carbocyclyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10} alkynyl, C_{3-12}carbocyclyl or C_{3-12}heterocyclyl, each of which being optionally substituted by one or more, same or different substituents represented by R_7, and the other is hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4} alkylthio, C_{1-6}alkylamino, C_{1-4}alkoxycarbonyl, cyano, -$CONH_2$ or nitro,

with the proviso that when R_5 or R_6 is phenyl, C_{1-5}alkyl or C_{2-3}alkenyl, it is substituted by one or more, same or different substituents represented by R_7 (except fluorine when R_5 or R_6 is methyl);

Y_2 is -O-, -S-, -S(O)-, -$S(O)_2$-, -NR_a-, -$NR_aC(O)NR_b$-, -$NR_aC(O)$-, -$C(O)NR_a$-, -$C(O)NR_aO$-, -C(O)-, -$NR_aC(O)O$- or -$NR_aS(O)_2$-;

R_9 is C_{1-10}alkyl-heterocyclyl, C_{1-10}alkyl-C_{3-12}carbocyclyl, C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10} alkynyl, C_{3-12}carbocyclyl or heterocyclyl, each being optionally substituted by one or more, same or different substituents represented by R_7, with the proviso that when Y_2 is –O-, -NR_a- or –S-, and R_9 is C_{1-6}alkyl, it is substituted by one or more, same or different substituents represented by R_7;

or, when one of R_5 or R_6 is the group –$C(O)NR_aR_9$, R_a and R_9 together with the nitrogen atom to which they are attached form a heterocyclic ring optionally comprising one or more additional heteroatoms selected from the group consisting of O, S and N, optionally substituted with one or more substituents represented by R_7;

or a pharmaceutically acceptable salt or ester thereof.

2. A compound according to claim 1, wherein R_1 is halogen, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or nitro.

3. A compound according to claim 2, wherein R_1 is methyl, ethyl, methoxy, ethoxy, bromo, fluoro or chloro.

4. A compound according to any one of claims 1-3, wherein R_2 is halogen, amino, C_{1-4}alkyl or C_{1-4}alkoxy.

5. A compound according to claim 4, wherein R_2 is methyl, ethyl, methoxy, ethoxy, bromo, fluoro or chloro.

6. A compound according to any one of claims 1-5, wherein R_3 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy.

7. A compound according to claim 6, wherein R_3 is methyl, ethyl, methoxy, ethoxy, bromo, fluoro or chloro.

8. A compound according to any one of claims 1-7, wherein Y_1 is -O-, $-NR_a-$, $-NR_aC(O)NR_b-$, $-NR_aC(O)-$, $-C(O)NR_a-$ or $-NR_aC(O)O-$.

9. A compound according to any one of claims 1-8, wherein R_8 is C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl.

10. A compound according to any one of claims 1-9, wherein R_7 is halogen, hydroxy, amino, C_{1-4}alkoxy, C_{1-4}alkyl, C_{1-4}alkylamino, C_{1-4}alkoxycarbonyl, -COOH, $-CONH_2$, -CONR' or -CONRR', wherein R and R' are as indicated in claim 1.

11. A compound according to any one of claims 1-10, wherein one of R_5 and R_6 is Y_2R_9, C_{1-4}alkyl-Y_2R_9, C_{1-4}alkenyl-Y_2R_9, C_{1-4}alkyl-C_{3-6}heterocyclyl, C_{1-4}alkyl-C_{3-6}carbocyclyl, C_{1-4}alkyl substituted by R_7, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl, and the other is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy.

12. A compound according to claim 11, wherein R_5 is Y_2R_9, C_{1-4}alkyl-Y_2R_9, C_{1-4}alkenyl-Y_2R_9, C_{1-4}alkyl-C_{3-6}heterocyclyl, C_{1-4}alkyl-C_{3-6}carbocyclyl, C_{1-4}alkyl substituted by R_7, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl, and the other is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy.

13. A compound according to claim 12, wherein R_6 is hydrogen.

14. A compound according to any one of claims 11-13, wherein Y_2 is -O-, $-NR_a-$, $-NR_aC(O)NR_b-$, $-NR_aC(O)-$, $-C(O)NR_a-$, $-C(O)NR_aO-$, -C(O)- or $-NR_aC(O)O-$.

15. A compound according to any one of claims 11-14, wherein R_9 is C_{1-4}alkyl-C_{3-6} heterocyclyl, C_{1-4}alkyl-C_{3-6}carbocyclyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl.

16. A compound according to any one of claims 1-15, wherein

R_1 is halogen, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or nitro;

R_2 is halogen, amino, C_{1-4}alkyl or C_{1-4}alkoxy;

R_3 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy;

Y_1 is –O-, $-NR_a-$, $-NR_aC(O)NR_b-$, $-NR_aC(O)-$, $-C(O)NR_a-$ or $-NR_aC(O)O-$;

R_8 is C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl;

R_7 is halogen, hydroxy, amino, C_{1-4}alkoxy, C_{1-4}alkyl, C_{1-4}alkylamino, C_{1-4}alkoxycarbonyl, -COOH, $-CONH_2$, -CONR' or –CONRR', wherein R and R' are as indicated in claim 1;

R_5 is Y_2R_9, C_{1-4}alkyl-Y_2R_9, C_{1-4}alkenyl-Y_2R_9, C_{1-4}alkyl-C_{3-6}heterocyclyl, C_{1-4}alkyl-C_{3-6}carbocyclyl, C_{1-4}alkyl substituted by R_7, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl, and R_6 is hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy;

Y_2 is -O-, $-NR_a-$, $-NR_aC(O)NR_b-$, $-NR_aC(O)-$, $-C(O)NR_a-$, $-C(O)NR_aO-$, -C(O)- or $-NR_aC(O)O-$; and

R_9 is C_{1-4}alkyl-C_{3-6} heterocyclyl, C_{1-4}alkyl-C_{3-6}carbocyclyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6}carbocyclyl or C_{3-6}heterocyclyl.

17. A compound according to any one of claims 1-15 selected from the group consisting of

[2-Chloro-4-(4-fluoro-2-methylphenylamino)phenyl]-[2-methyl-5-(morpholine-4-carbonyl)phenyl]methanone (Compound 101),

[2-Chloro-4-(4-fluoro-2-methylphenylamino)phenyl]-[2-methyl-5-(4-methylpiperazine-1-carbonyl)phenyl]methanone (Compound 102),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-*N*-methoxy-4,*N*-dimethylbenzamide (Compound 103),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-(tetrahydrofuran-2-ylmethyl)benzamide (Compound 104),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4,*N*-dimethyl-*N*-(tetrahydrofuran-2-ylmethyl)benzamide (Compound 105),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-*N*-(2-methoxyethyl)-4-methylbenzamide (Compound 106),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-(3-morpholin-4-ylpropyl)benzamide (Compound 107),

[2-Chloro-4-(4-fluoro-2-methylphenylamino)phenyl]-{5-[4-(2-methoxyethyl)piperazine-1-carbonyl]-2-methylphenyl}methanone (Compound 108),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-pyridin-4-ylmethylbenzamide (Compound 109),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-pyridin-2-ylmethylbenzamide (Compound 110),

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-4-methyl-*N*-pyridin-3-ylmethyl-benzamide (Compound 111),

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 112),

3-[4-(2-Amino-4-bromophenylamino)-2-chlorobenzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 113),

3-[4-(4-Bromo-2-methylphenylamino)-2-chlorobenzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 114),

3-[2-Chloro-4-(2,4-difluorophenylamino)benzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 115),

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-(2-methoxyethyl)-4-methylbenzamide (Compound 116),

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-ethyl-4-methylbenzamide (Compound 117),

3-[4-(2-Aminophenylamino)-2-chlorobenzoyl]-*N*-(3-hydroxypropyl)-4-methylbenzamide (Compound 118), and

3-[2-Chloro-4-(4-fluoro-2-methylphenylamino)benzoyl]-*N*-(2-hydroxyethyl)-4-methylbenzamide (Compound 119),

18. A pharmaceutical composition comprising a compound according to any one of claims 1-17 or a pharmaceutically acceptable salt or ester thereof together with a pharmaceutically acceptable vehicle or excipient.

19. A composition according to claim 18 further comprising another active component selected from the group consisting of glucocorticoids, vitamin D analogues, anti-histamines, platelet activating factor (PAF) antagonists, anticolergenic agents, methyl xanthines, β-adregenic agents, COX-2 inhibitors, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, peniciliamine, serum cholesterol reducing agents, retinoids, zinc salts and salicylazosulfapyridin.

20. A compound according to any one of claims 1-17 for use as a medicament.

21. A compound according to any one of claims 1-17 for use as an anti-inflammatory agent.

22. Use of a compound according to any one of claims 1-17 for the manufacture of a medicament for the prophylaxis, treatment or amelioration of inflammatory diseases or conditions.

23. Use of a compound according to any one of claims 1-17 for the manufacture of a medicament for the treatment or amelioration of cancer.

24. The use of claim 22, wherein the medicament is intended for administration together with another active component selected from the group consisting of glucocorticoids, vitamin D analogues, anti-histamines, platelet activating factor (PAF) antagonists,

anticholinergenic agents, methyl xanthines, β-adregenic agents, COX-2 inhibitors, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, peniciliamine, serum cholesterol reducing agents, retinoids, zinc salts and salicylazosulfapyridin.

25. The use of claim 22 or 24, wherein the inflammatory disease or condition is asthma, allergy, arthritis, rheumatoid arthritis, spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease, Crohn's disease, neurological inflammations, inflammatory eye diseases, proliferative and inflammatory skin disorders, psoriasis, atopic dermatitis, acne, uveitis, sepsis, septic shock or acne, osteoporosis.

26. A method of preventing, treating or ameliorating inflammatory diseases or conditions, the method comprising administering to a patient in need thereof an effective amount of a compound according to any one of claims 1-17.

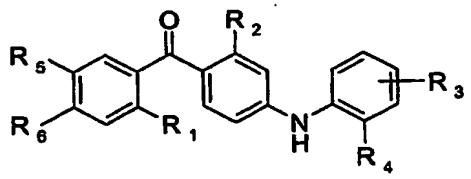
27. A method of treating or ameliorating cancer, the method comprising administering to a patient in need thereof an effective amount of a compound according to any one of claims 1-17.

28. The method of claim 26 further comprising administering another active component selected from the group consisting of glucocorticoids, vitamin D analogues, anti-histamines, platelet activating factor (PAF) antagonists, anticholinergenic agents, methyl xanthines, β-adregenic agents, COX-2 inhibitors, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, peniciliamine, serum cholesterol reducing agents, retinoids, zinc salts and salicylazosulfapyridin.

29. The method of claim 26 or or 28, wherein the inflammatory disease or condition is asthma, allergy, arthritis, rheumatoid arthritis, spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease, Crohn's disease, neurological inflammations, inflammatory eye diseases, proliferative and inflammatory skin disorders, psoriasis, atopic dermatitis, acne, uveitis, sepsis, septic shock or acne, and osteoporosis.

ABSTRACT

The invention provides novel compounds according to formula I relates to compounds with the general formula I



I

said compounds being useful, e.g. in the treatment of inflammatory diseases or cancer.